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The effects of treatment with felodipine as a single agent in coronary artery disease

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SUMMARY In an earlier study one dose of the vasodilator felodipine improved haemodynamic function in patients with angina without having a negative inotropic effect. The haemodynamic response of sustained treatment with felodipine as a single agent in stable angina was investigated in a double blind crossover study of 25 patients. The dosage of felodipine was increased from 5 mg twice daily to 10 mg twice daily after two weeks. Twenty one patients completed the study, two were withdrawn because of acute myocardial infarction, and a further two because of symptoms of vasodilatation. Felodipine reduced both supine and erect blood pressure and increased the resting heart rate. Median exercise time was increased by 10% at two weeks and 7% at four weeks. There was a sustained reduction in the number of angina attacks and use of sublingual nitrate on active treatment.

Felodipine has antianginal effects but these are limited and seem less than those of other related compounds. This finding is unexpected and possibly related to increased heart rate.

Felodipine, a dihydropyridine, is a new vasodilating agent which reduces blood pressure, increases stroke volume, and in a single dose study increased exercise capacity.[1] It has also been shown to be a useful adjunctive agent to β blockade in stable angina.[2] To investigate the potential beneficial effects of longer term treatment we studied the effects of an increasing dose of felodipine on exercise tolerance, symptoms, and the haemodynamic response to exercise.

Patients and methods

We studied 25 patients (17 men and eight women, aged 40–65 years (mean 52·0)) who had had stable angina for at least two months with at least five attacks per week. All patients had an initial positive exercise test with at least 1 mm of ST depression associated with chest pain. They gave their informed consent to the study. Fertile women were excluded. We also excluded patients with important valve disease, myocardial infarction within the past two months, unstable angina, systolic blood pressure < 100 mm Hg, insulin dependent diabetes, a history of severe allergic response, or severe hepatic failure.

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All medication other than sublingual nitrates was stopped for at least two weeks before the start of the study. Seven patients had already been treated with nifedipine and three with atenolol.

The study had three parts—a run in period of two weeks on placebo followed by two double blind crossover periods of four weeks on felodipine or placebo. After two weeks we increased the dose of either felodipine or placebo from 5 mg twice a day to 10 mg twice a day if no adverse features had occurred. The tablets taken during the felodipine and placebo treatment periods were dispensed in computer generated random order. After the first and second two week periods the patients performed a symptom limited Bruce protocol exercise test and had a clinical examination with history. The erect and supine blood pressure and pulse were carefully recorded. All exercise tests were performed between 1 and 3 hours after the last dose of the study medication. Plasma samples were taken for felodipine analysis at each visit during the crossover period.

At each visit the patients were given a diary card to record the number of angina attacks and consumption of sublingual nitrate. At the end of the study the patients returned to their usual medication.

Results are expressed as median or mean and were analysed by Wilcoxon matched pairs signed ranks test and Student's t test; a probability value of $< 0{\cdot}05$ was regarded as statistically significant.

Results

Twenty one patients completed the study. Of the four patients who were withdrawn from the study: one experienced severe abdominal pain while on placebo, one complained of flushing and burning of her feet, legs, and face while taking felodipine, and an acute myocardial infarction developed while two patients were taking felodipine 5 mg twice daily. After two weeks' treatment, 11 patients had their dosage increased from 5 mg twice daily to 10 mg twice daily but in one patient the dose was subsequently reduced because minor side effects of vasodilatation developed.

At the end of the double blind periods 11 patients were taking felodipine 5 mg twice daily, 10 patients were taking 10 mg twice daily, and 10 and 11 patients were taking 5 mg and 10 mg of placebo respectively. Plasma analysis showed that two additional patients had appreciable concentrations of plasma felodipine when they should have been taking placebo. We excluded their data from subsequent analysis. Data from the remaining 19 patients were analysed.

Supine and erect blood pressure were lower during felodipine treatment than during placebo treatment. The mean reductions after two weeks' treatment with felodipine were 8/7 mm Hg ($p < 0.01$) and 8/4 mm Hg ($p < 0.05$/NS) respectively. The corresponding figures after four weeks' treatment were 3/5 mm Hg (NS/$p < 0.05$) and 7/6 mm Hg ($p < 0.05$/NS). After four weeks of felodipine treatment the mean heart rate in supine patients increased slightly (6 beats/min ($p < 0.05$)). After two weeks of felodipine treatment the median duration of exercise was 10% higher than during placebo treatment ($p < 0.05$). The increase (7%) after four weeks was not statistically significant (table 1). When patients were taking felodipine 5 mg twice a day the mean (SD) heart rate at maximal exercise was increased by seven beats per minute (from 144 (12) to 151 (13) NS), systolic blood pressure was reduced from 165 (19) to 159 (19) mm Hg (NS), and the mean (SD) rate-pressure product was essentially unchanged (from 24500 (3700) to 23900 (3300)). When patients were taking felodipine 10 mg twice a day, the mean (SD) heart rate increased from 149 (14) to 150 (14), the systolic blood pressure was reduced from 158 (15) to 154 (18) mm Hg (NS), and the rate-pressure product was again essentially unchanged (from 23700 (3100) to 23400 (3300)). We did not find a significant relation between ST depression and the rate-pressure product at maximal exertion, although median ST depression was reduced after two weeks' treatment with felodipine (2 to 1·8 mm, $p < 0.05$) but not after four weeks.

The diary cards showed a sustained tendency towards fewer angina attacks and reduced consumption of glyceryl trinitrate during treatment with felodipine (NS) (tables 2 and 3). Both systolic and diastolic blood presure fell significantly after exercise, particularly at 10 minutes (8/7 mm Hg, $p < 0.01/p < 0.05$). The heart rate was also significantly increased after exercise, especially after four weeks' treatment with felodipine (at 10 minutes it was 11 beats per minute higher ($p < 0.001$)). No clinically significant differences in mean body weight, angle circumference, or haematological or biochemical values were noted.

Discussion

The efficacy of calcium antagonist vasodilator agents in treating symptomatic coronary artery disease is well established both on their own and in combination with other agents such as β blockers. Most of these agents have negative inotropic effects, which can limit their usefulness; none the less, felodipine has been shown to increase cardiac output[3,4] and to increase resting myocardial blood flow.[3] Interest has therefore been expressed in establishing its potential

Table 1 *Exercise duration(s) in different treatment groups*

	Placebo after 2 weeks		*Felodipine after 2 weeks*	*Placebo after 4 weeks*		*Felodipine after 4 weeks*
			Felodipine 5 mg twice a day at 2 and 4 weeks			
n	11		11	11		11
Mean (SD)	514 (148)		558 (127)	556 (131)		588 (148)
Median	505	NS	586	540	NS	595
			Felodipine 5 mg twice a day at 2 weeks and 10 mg twice a day at 4 weeks			
n	8		8	8		8
Mean (SD)	510 (176)		574 (141)	537 (163)		545 (123)
Median	528	NS	584	538	NS	530
			Totals			
n	19		19	19		19
Mean (SD)	524 (157)		565 (134)	548 (145)		570 (140)
Median	505	$p < 0.05$	586	540	NS	568

Table 2 *Number of angina attacks per week in different treatment groups*

	Placebo after 2 weeks		*Felodipine after 2 weeks*	*Placebo after 4 weeks*		*Felodipine after 4 weeks*
			Felodipine 5 mg twice a day at 2 and 4 weeks			
n	11		11	10		10
Mean (SD)	2·8 (1·9)		2·2 (3·2)	5·6 (6·4)		2·2 (3·0)
Median	2·7	NS	1·0	2·2	NS	0·8
			Felodipine 5 mg twice a day at 2 weeks and 10 mg twice a day at 4 weeks			
n	8		8	8		8
Mean (SD)	6·2 (8·2)		5·2 (3·5)	5·3 (5·1)		3·2 (2·6)
Median	3·0	NS	4·8	4·8	NS	2·3
			Totals			
n	19		19	18		18
Mean (SD)	4·2 (5·8)		3·4 (3·6)	5·0 (5·7)		2·8 (2·9)
Median	2·7	NS	2·0	2·9	NS	1·4

for treating patients with coronary artery disease.

Single doses of felodipine increased maximal cardiac output by 20% and the maximal pressure-rate product by 13%.[1] The relation between ST segment depression and the rate-pressure product during exercise was also favourably influenced. In a further study in which felodipine was added to conventional β blockade there was a significant improvement in exercise tolerance and daily attacks of angina.[2]

In our study although there was a similar improvement in exercise tolerance after two weeks' treatment, at four weeks the benefit was less apparent. This reduced benefit is not entirely unexpected because felodipine, in common with other peripheral vasodilators, induces reflex sympathetic activity thereby increasing heart rate and myocardial oxygen consumption, with a consequent effect on the drug's antianginal action. Both supine and erect blood pressure fell significantly as would be expected with a drug causing peripheral arteriolar vasodilatation.

Despite the increase in dosage in eight (42%) of the 19 patients at four weeks the effect of felodipine on mean exercise capacity was not as strong as at two weeks. There are two possible explanations for this. Firstly a ceiling may have been reached at a dose of 5 mg twice a day, which suggests that the drug may have a flat dose response curve. This explanation is supported by the apparent lack of additional effect on the resting supine and erect blood pressure, median ST depression, and rate-pressure product at maximal exercise after increasing the dosage to 10 mg twice a day. Secondly, the training effect of repeated exercise tests could improve the results of both treatment groups; however, as the baseline exercise tolerance improves, the statistical significance of the measured improvement is reduced. As only 42% of the patients had their felodipine increased to 10 mg twice a day, subgroup analysis of patients taking 5 mg and 10 mg twice a day after 4 weeks has to be interpreted with caution in view of the relatively small numbers. Although an increase in the dosage of felodipine from 5 mg to 10 mg twice daily did not improve exercise tolerance or the rate-pressure product at maximal exercise, the number of weekly angina attacks was halved. The number of side effects reported was low and related to the vasodilatory properties of the drug.

Table 3 *Use of sublingual glyceryl trinitrate in different treatment groups (tablets (0·5 mg) per week)*

	Placebo after 2 weeks		*Felodipine after 2 weeks*	*Placebo after 4 weeks*		*Felodipine after 4 weeks*
			Felodipine 5 mg twice a day at 2 and 4 weeks			
n	11		11	10		10
Mean (SD)	2·4 (2·7)		0·7 (0·8)	2·0 (2·0)		0·8 (1·4)
Median	1·5	$p = 0·01$	0·5	1·0	NS	0·0
			Felodipine 5 mg twice a day at 2 weeks and 10 mg twice a day at 4 weeks			
n	8		8	8		8
Mean (SD)	4·8 (6·9)		3·1 (2·6)	4·0 (3·6)		2·1 (2·4)
Median	2·5	NS	3·5	3·8	NS	1·3
			Totals			
n	19		19	18		18
Mean (SD)	3·0 (4·9)		1·7 (2·1)	2·9 (3·0)		1·4 (2·0)
Median	2·0	NS	0·5	1·6	$p < 0·05$	0·9

The first patient who experienced a myocardial infarction while taking felodipine had a poor initial exercise tolerance of 207 seconds and approximately three attacks of angina per day associated with exercise. During felodipine treatment exercise tolerance fell to 190 seconds and the number of anginal attacks increased by 16%. It is possible that in this patient the drug contributed to the development of these adverse features because it resulted in unopposed reflex sympathetic activity (thereby increasing myocardial oxygen consumption[2] or because it induced a coronary artery steal phenomenon. When it is used alone, nifedipine (a related dihydropyridine) can induce angina; the mechanism for this effect is not known.[5] The second patient with a myocardial infarction had satisfactory initial exercise tolerance and approximately one anginal attack per week. Because he improved substantially on felodipine the development of infarction was unexpected, and it seems unlikely that it was related to the drug. This study shows that felodipine has antianginal properties in patients with coronary artery disease but these seem to be limited and less than those of other reported compounds such as nifedipine.[6,7] It may be especially suitable for patients with angina and hypertension in whom its ability to maintain or increase the cardiac output is an advantage.[4,8]

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